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<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/557 // (A61K 31/557, 31:415, 31:27)</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/23226</b> <b>(43) International Publication Date:</b> 3 July 1997 (03.07.97)
<b>(21) International Application Number:</b> PCT/US96/18888 <b>(22) International Filing Date:</b> 25 November 1996 (25.11.96)  <b>(30) Priority Data:</b> 08/577,038 22 December 1995 (22.12.95) US  <b>(71) Applicant:</b> ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134-2099 (US).  <b>(72) Inventor:</b> DEAN, Thomas, Robert; 101 Meadow View Court, Weatherford, TX 76087 (US).  <b>(74) Agents:</b> YEAGER, Sally, S. et al.; Alcon Laboratories, Inc., Patent Dept. Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).	<b>(81) Designated States:</b> AU, CA, JP, MX, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>	
<b>(54) Title:</b> COMBINATIONS OF PROSTAGLANDINS AND MIOTICS FOR LOWERING INTRAOCULAR PRESSURE  <b>(57) Abstract</b>  Methods for controlling glaucoma or ocular hypertension with combinations of DP-agonists and miotics are disclosed.		

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IN THE UNITED STATES PATENT  
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COMBINATIONS OF PROSTAGLANDINS AND MIOTICS  
FOR LOWERING INTRAOCULAR PRESSURE

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This invention is directed to methods for treating persons suffering from glaucoma or ocular hypertension.

**Background of the Invention**

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Although the underlying causes of glaucoma are not well understood, its symptoms often include elevated intraocular pressure (IOP) which arises due to inadequate outflow of aqueous humor through the trabecular meshwork. Also, ocular hypertension, a condition characterized by elevated IOP, can be a risk factor in the development of glaucoma. If left untreated, or if inadequately treated, glaucoma can lead to blindness or significant vision loss. Therefore, there is a continuing need for therapies which control elevated IOP associated with glaucoma or ocular hypertension.

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There are currently a number of drugs used to treat persons with glaucoma, including: miotics (e.g., pilocarpine, carbachol, and acetylcholinesterase inhibitors); sympathomimetics (e.g., epinephrine and dipivalylepinephrine); alpha-2 agonists (e.g., para-amino clonidine); beta-blockers (e.g., betaxolol, levobunolol, and timolol); and carbonic anhydrase inhibitors (e.g., acetazolamide, methazolamide, and ethoxzolamide systemically and dorzolamide topically). Miotics and sympathomimetics are believed to lower IOP by increasing the outflow of aqueous humor through the trabecular meshwork, while beta-blockers, alpha-2 agonists, and carbonic anhydrase inhibitors are believed to lower IOP by decreasing the formation of aqueous humor.

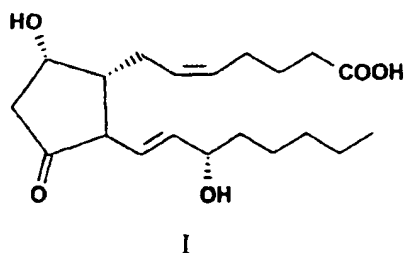
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In addition, although none have yet been approved for anti-glaucoma therapy, certain classes of prostaglandins and prostaglandin analogues (hereinafter collectively referred to as "prostaglandins") have been shown in various animal models and in some clinical studies to reduce IOP to a greater extent than most currently used therapeutic agents. See, for example: U.S. Patent Nos. 4,097,489; 4,599,353; 5,296,504; WO 90/02553; EP 569 046A1; EP 364 417B1; U.S. Patent No. 4,994,274; and EP 289 349. In contrast to the case with miotics which affect conventional outflow, i.e., via the trabecular meshwork, some prostaglandins are believed to lower IOP by increasing the outflow of aqueous humor via the uveo-scleral route.

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Prostaglandins are metabolite derivatives of arachidonic acid. The arachidonic acid cascade is initiated by the conversion of arachidonic acid to prostaglandin  $G_2$  and subsequent conversion to prostaglandin  $H_2$ . Other naturally occurring prostaglandins are derivatives of prostaglandin  $H_2$ . A number of different types of prostaglandins have been discovered including A, B, D, E, F and I-Series prostaglandins. Of interest in the present invention are compounds which exhibit similar IOP lowering mechanisms as  $PGD_2$  with the following formula:

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The relationship of PGD<sub>2</sub> receptor activation and IOP lowering effects is not well known. Various publications have reported that PGD<sub>2</sub> receptor activation leads to second messenger activation and in particular, to the stimulation of adenylate cyclase and resultant increases in cAMP levels (Thierauch, "Prostaglandins and their Receptors: II. Receptor Structure and Signal Transduction," *Journal of Hypertension*, 12:1-5 (1994). Regardless of mechanism, PGD<sub>2</sub> has been shown to lower IOP (Nakajima, "Effects of Prostaglandin D<sub>2</sub> and its analogue, BW245C, on Intraocular Pressure in Humans," *Graefe's Archive Ophthalmology*, 229:411-413 (1991)).

Synthetic PGD<sub>2</sub>-type analogs have been pursued in the art (*Graefe's Archive Ophthalmology*, 229:411-413 (1991)). Though PGD<sub>2</sub>-type molecules help lower IOP, these types of molecules have also been associated with undesirable side effects resulting from topical ophthalmic dosing. Such effects include an initial increase in IOP, conjunctival hyperemia, increases in microvascular permeability, and increases in eosinophile infiltration (Alm, "The Potential of Prostaglandin Derivatives in Glaucoma Therapy," *Current Opinion in Ophthalmology*, 4(11):44-50 (1993)).

It has been unexpectedly been found that 3-Oxa-D-prostaglandins ("3-O-DP") are more efficacious in lowering and controlling IOP than their 3-carba analogs. Consequently, these 3-O-DPs can be administered at lower doses than their 3-carba analogs. The lower doses are believed to reduce their activity on other prostaglandin receptors and thereby reduce many of the aforementioned undesirable side effects.

All six types of therapeutic agents discussed above have potentially serious side effects. Miotics, such as pilocarpine, can cause ocular discomfort, headaches, and blurred vision, which may lead either to decreased patient compliance or to termination of therapy. Systemically dosed carbonic anhydrase inhibitors can also cause serious side effects, such as, 5 nausea, dyspepsia, fatigue, and metabolic acidosis, which affect patient compliance and/or necessitate the withdrawal of treatment. Some beta-blockers have increasingly become associated with serious pulmonary side effects attributable to their effect on beta-2 receptors in pulmonary tissue. Prostaglandins often produce hyperemia and edema of the conjunctiva.

10 Patients with extremely high IOP require a therapy regimen which includes the use of two or more pharmaceutical compositions containing drugs selected from two or more of the above-cited classes. There is a continuing need for new, more potent anti-glaucoma therapies. The present invention is directed to such therapies.

### 15 **Summary of the Invention**

The present invention is directed to the use of DP-agonists (hereinafter defined) and miotics, particularly pilocarpine, for treating persons suffering from glaucoma or ocular hypertension.

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### **Description of Preferred Embodiments**

Many people suffering from glaucoma or ocular hypertension cannot control their elevated IOP using only one of the therapeutic agents described above. It is believed that the 25 use of a miotic, such as pilocarpine or an analogue of pilocarpine (hereinafter collectively referred to as "pilocarpine"), in combination with a DP-agonist will be effective in controlling the IOP in those persons for which one therapeutic agent is not enough.

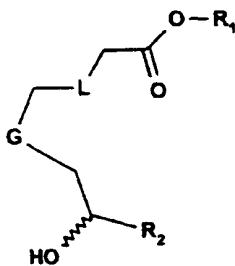
As previously discussed miotics are known to lower IOP by increasing outflow via the trabecular meshwork. DP-agonists may affect IOP by decreasing aqueous humor production (decreasing inflow). Thus, the use of a miotic, such as pilocarpine, carbachol, or acetylcholinesterase inhibitors, preferably pilocarpine, in combination with a prostaglandin  
5 that decreases aqueous humor production will better lower and control elevated IOP in persons suffering from ocular hypertension or glaucoma.

The DP-agonists of the present invention are useful in lowering IOP in humans and other mammals. They are functionally defined by their ability to bind to prostaglandin-D<sub>2</sub>  
10 receptors of cells and evoke similar responses as when PGD<sub>2</sub> binds to these receptors, including the lowering of IOP. Various assays may be used for the determination of DP-agonists.

Binding assays may be used to elucidate DP-agonists of the present invention. Sharif  
15 has described a receptor binding assay in: Sharif, N.A., Williams, G.W. and DeSantis, L.M., *Neurochemistry Research*, 20:669-674 (1994), the entire contents of which are incorporated herein by reference, and may be modified for the elucidation of DP-agonists of the present invention. Briefly, the binding assays are conducted in 25 mM Tris HCl (pH 7.4) containing 138 mM NaCl, 5 mM MgCl<sub>2</sub>, and 1 mM EDTA. Frozen-thawed expired human blood  
20 platelets (40-60 mg/ml stock) are incubated in a total volume of 500  $\mu$ l with 2-10 nM [<sup>3</sup>H]PGD<sub>2</sub> in the absence and presence of 100  $\mu$ M unlabeled PGD<sub>2</sub> to define total and non-specific binding, respectively. The incubations (20 minutes at 23°C) are terminated by rapid vacuum filtration, using a Whatman GF/B glass fiber filter previously soaked in 1% polyethyleneimine and 0.1% BSA, and the receptor-bound radioactivity is then determined by  
25 scintillation spectrometry. The binding data are analyzed using a non-linear, iterative curve-fitting computer program to define the receptor binding affinity (K<sub>i</sub>) of the compounds. Compounds which exhibit K<sub>i</sub> values in this assay of less than or equal to about 20  $\mu$ M are within the definition of DP-agonists of the present invention.

The DP-agonists of the present invention are defined functionally, by their ability to stimulate adenylate cyclase activity. Sharif has described one type of functional assay in: Sharif, N.A., Xu, S. and Yanni, J.M. *Journal of Ocular Pharmacology*, 10:653-664 (1994), the entire contents of which are incorporated herein by reference and may be modified for the elucidation of DP-agonists of the present invention. Briefly, functional adenylate cyclase activity is determined using embryonic bovine tracheal cells (EbTr) cells. Cultured cells are stimulated with the test compound for 15 minutes at 23°C. The reaction is then stopped and the cAMP generated is determined by a radioimmunoassay kit. Data are analyzed using a non-linear, iterative curve-fitting computer program to define the potency ("EC<sub>50</sub>", concentration which produces 50% of the maximum response of PGD<sub>2</sub>) and efficacy of the compounds. Compounds which exhibit EC<sub>50</sub> values of less than or equal to about 10 µM are within the DP-agonist definition of the present invention.

Preferred DP-agonists of the present invention are of the following formula (II):



II

wherein:

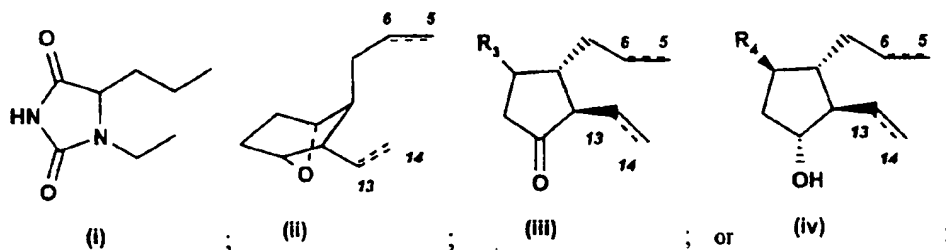
R<sub>1</sub> is H, alkyl or alkylcyloalkyl;

R<sub>2</sub> is alkyl, cycloalkyl or alkylcycloalkyl;

L is carbon or oxygen; and



G is



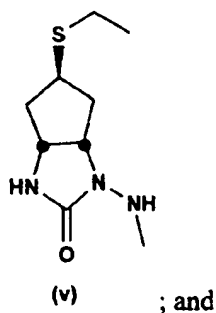
wherein:

$R_3$  is H, OH or alkyl;

$R_4$  is H, F, Cl, I, or  $C_{1-3}$  alkyl;

== represents a single bond or double bond; provided that when a double bond is between the 13 and 14 position it is in the *trans* configuration;

when L is carbon, G may also be



pharmaceutically acceptable salts thereof.

Preferred DP-agonists of the present invention are those of formula (II), wherein one or more of the following substituents is selected:

G is (ii) and (iv);

$R_4$  is Cl;

R<sub>2</sub> is cyclohexyl;

L is oxygen;

R<sub>1</sub> is isopropyl; and

the bond between the 5 and 6 position is a *cis* configured double bond.

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The most preferred DP-agonist is when G is (iv); R<sub>4</sub> is Cl; R<sub>2</sub> is cyclohexyl; L is oxygen; R<sub>1</sub> is isopropyl, the bond between position 13 and 14 is saturated; and the bond between the 5 and 6 position is a *cis* configured double bond.

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Some of the DP-agonists of the present invention may be novel.

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The DP-agonist of the present invention, aside from those compounds which may be novel, are known to those skilled in the art, and available commercially or may be made by methods known to those skilled in the art. Novel compounds of the present invention may be prepared by analogous synthetic routes as those which are known.

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The DP-agonists wherein G is formula (i), are described in Barraclough, "Synthesis and Platelet Aggregation Inhibiting Activity of Acid Side-chain Modified Hydantoin Prostaglandin Analogues," *Archives in Pharmacology*, 326(2):85-95 (1993), the entire contents of which are incorporated herein by reference.

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The DP-agonists wherein G is formula (ii), may be prepared from [1*S*-[1 $\alpha$ , 2 $\alpha$ (*Z*), 3 $\alpha$ (1*E*, 3*S*), 4 $\alpha$ ]]-7-[3-(3-Cyclohexyl-3-hydroxy-1-propenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid following the procedure described in Das, "9,11-Epoxy-9-homoprostanoic Acid Analogues as Thromboxane A<sub>2</sub> Receptor Antagonists," *Journal of Medicinal Chemistry*, 33(6):1741-1748 (1990), for the conversion of [1*S*-[1 $\alpha$ , 2 $\alpha$ (*Z*), 3 $\alpha$ (1*E*, 3*S*, 4*R*)), 4 $\alpha$ ]]-7-[3-[4-phenyl-3-(tetrahydropyran-2-yloxy)-1-pentyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

to [1S-[1 $\alpha$ , 2 $\alpha$ (Z), 3 $\alpha$  (1E, 3S, 4R)), 4 $\alpha$ ]]-[[4-[3-(3-hydroxy-4-phenyl-1-pentyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid.

The DP-agonists wherein G is formula (iii), may be prepared from (5Z, 13E)-9S, 11R, 15S)-15 cyclohexyl-9-hydroxy-3-oxa-11,15-bis (tetrahydropyran-2-yloxy)-16, 17, 18, 19, 20-pentanol -5,13-prostanoic acid tert butyl ester (EP 299 914) by the method described in Bundy, "Synthesis and Platelet Aggregation Inhibiting Activity of Prostaglandin D Analogues," *Journal of Medicinal Chemistry*, 26:790-799 (1983), the entire contents of which are incorporated herein by reference.

The DP-agonists wherein G is formula (iv) are disclosed in WO 94/05631, and is incorporated herein by reference to the extent this publication teaches the synthesis of the compounds contained therein.

The DP-agonists of the present invention wherein G is (v) are disclosed in European Patent Application Publication No. 0 458 642 A1, and is incorporated herein by reference to the extent this publication teaches the synthesis of the compounds contained therein.

The combinations of DP-agonists and miotics according to the present invention are useful in lowering intraocular pressure and thus are useful in the treatment of persons suffering from ocular hypertension or glaucoma. As compared with therapeutically effective dosages of the individual components, the combinations produce significantly fewer unwanted side effects such as marked vasoconstriction or vasodilation of the vessels of the sclera, painful stinging, and intraocular inflammation.

The DP-agonists and miotics of the present invention may be formulated in various pharmaceutical compositions for simultaneous, sequential, or offset combinatorial administration to humans and other mammals as a prophylaxis or treatment of glaucoma or

ocular hypertension. For example, the DP-agonists and the miotics may be formulated together in one composition for simultaneous administration. Alternatively, they may be formulated separately for 1) concomittant dosing; 2) short delay dosing between one agent and the other; or 3) offset dosing, such as a DP-agonist dosing at night and the miotic dosed in the morning and evening.

The preferred route of administration of the compositions is topical. As used herein, the term "pharmaceutically effective amount" refers to that amount of a DP-agonist or miotic or combination of a DP-agonist and miotic which lowers IOP when administered to a mammal. The compounds of the present invention can be administered as solutions, suspensions, or emulsions (dispersions) in a suitable ophthalmic vehicle.

In forming compositions for topical administration, the DP-agonists of the present invention are generally formulated at about 0.0003 to about 0.5 percent by weight (wt%) solutions in water at a pH between 4.5 to 7.4. The compounds are preferably formulated at about 0.0003 to about 0.3 wt% and, most preferably, at about 0.003 and about 0.03 wt%. The miotics of the present invention are generally formulated at about 0.5 to 10.0 wt.%, preferably 1.0 to 3.0 wt.%. While the precise regimen is left to the discretion of the clinician, it is recommended that the resulting solutions be topically applied by placing one drop in each eye one to four times a day.

Other ingredients which may be desirable to use in the ophthalmic preparations of the present invention include preservatives, solvents, and viscosity building agents.

Preferred formulations of the present invention include the following Examples 1-3:

**Example 1**

5	Ingredient	Amount (wt%)
	DP-Agonist	0.003
	Miotic	1.0
	Phosphate Buffered Saline	1.0
10	Polysorbate 80	0.5
	Purified water	q.s. to 100%

**Example 2**

An example of two formulations to be used concomitantly, within 30 minutes, or offset by more than 1 hour.

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**Formulation A**

Ingredient	Amount (wt%)
DP-Agonist	0.001
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA (Edetate disodium)	0.05
Cremophor EL	0.1
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.3 - 7.4
Purified water	q.s. to 100%

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**Formulation B**

	<b>Ingredient</b>	<b>Amount (wt%)</b>
5	Miotic	1.0
	Monobasic sodium phosphate	0.05
	Dibasic sodium phosphate (anhydrous)	0.15
	Sodium chloride	0.75
10	Disodium EDTA (Edetate disodium)	0.05
	Cremophor EL	0.1
	Benzalkonium chloride	0.01
	HCl and/or NaOH	pH 7.3 - 7.4
15	Purified water	q.s. to 100%

**Example 3**

Ingredient	Amount (wt%)
DP-Agonist	0.002
Pilocarpine	0.5
Phosphate Buffered Saline	1.0
Hydroxypropyl- $\beta$ -cyclodextrin	4.0
Purified water	q.s. to 100%

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The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

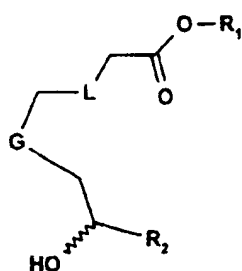
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**Claim:**

1. A method for controlling intraocular pressure in a person suffering from glaucoma or ocular hypertension, which comprises administration of a DP-agonist and a miotic.

2. The method of Claim 1 wherein the DP-agonist has the following formula:



II

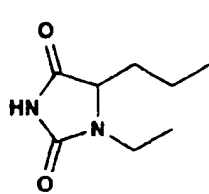
wherein:

R<sub>1</sub> is H, alkyl or alkylcycloalkyl;

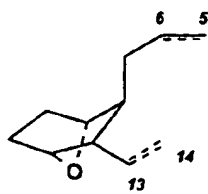
R<sub>2</sub> is alkyl, cycloalkyl or alkylcycloalkyl;

L is carbon or oxygen; and

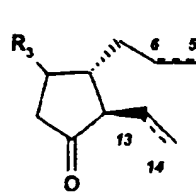
G is



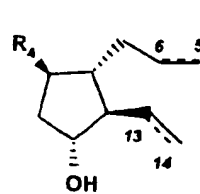
(i)



(ii)



(iii)



(iv)

; or

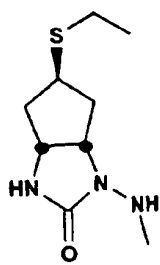
wherein:

R<sub>3</sub> is H, OH or alkyl;

R<sub>4</sub> is H, F, Cl, I, or C<sub>1-3</sub> alkyl;

--- represents a single bond or double bond; provided that when a double bond is between the 13 and 14 position it is in the *trans* configuration;

when L is carbon, G may also be



(v) ; and

pharmaceutically acceptable salts thereof.

3. The method of Claim 1 wherein the miotic is selected from the group consisting of pilocarpine, carbachol, and acetylcholinesterase inhibitors.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/18888

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/557 //(A61K31/557,31:415,31:27)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 458 642 A (WELLCOME FOUND) 27 November 1991 * see in particular claims 1-4, 14-15; page 4 lines 19-28, and page 5, lines 6-14	1-3
Y	* * *	1-3
X	--- EP 0 458 589 A (UENO SEIYAKU OYO KENKYUJO KK) 27 November 1991 * see in particular the claims, page 3, lines 43-49, and page 7, lines 3-46 *	1-3
Y	* * *	1-3
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

19 March 1997

Date of mailing of the international search report

16.04.97

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/18888

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WO 94 05631 A (SCHERING AG ;BUCHMANN BERND (DE); SKUBALLA WERNER (DE); EKERDT ROL) 17 March 1994  cited in the application  * see in particular page 13 (ultimate paragraph) page 14 *  -----</p>	1-3

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/18888

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		US 5147885 A	15-09-92
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